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10/509,675	09/13/2006	Piero Del Soldato	026220-00055	3644

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EXAMINER
LAU, JONATHAN S

ART UNIT	PAPER NUMBER
1623	

NOTIFICATION DATE	DELIVERY MODE
05/21/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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IPMatters@arentfox.com
Patent_Mail@arentfox.com

Office Action Summary	Application No.	Applicant(s)	
	10/509,675	DEL SOLDATO, PIERO	
	Examiner	Art Unit	
	Jonathan S. Lau	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *19 February 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) *2,5 and 6* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3, 4 and 7-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6 pgs / 08 Oct 2004* .
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application is the national stage entry of PCT/EP03/03183, filed 27 Mar 2003; and claims benefit of foreign priority document ITALY MI2002A00077, filed 11 Apr 2002. An English language translation of the foreign priority document is not currently of record.

Claims 1-9 are pending in the current application. Claims 2, 5 and 6, drawn to a nonelected species, are withdrawn. Claims 1, 3, 4 and 7-9 are examined on the merits herein. Claim 4 has been amended to correct minor informalities.

This Office Action is responsive to Applicant's amendment and remarks, filed 19 Feb 2008, in which the abstract, specification, and claim 4 have been amended to correct minor informalities.

Information Disclosure Statement

A translation of the abstract for DE 4420523 A1, cited on the IDS filed 08 Oct 2004 has received and has been considered by Examiner.

Objections Withdrawn

Applicant's amendment, filed 19 Feb 2008, with respect to the objections regarding the abstract of the disclosure has been fully considered and found to be persuasive to remove the objection as the amendment to remove "the" corrects the issue raised in this objection. Therefore this objection is **withdrawn**.

Applicant's amendment, filed 19 Feb 2008, with respect to the objections regarding the specification of the disclosure has been fully considered and found to be persuasive to remove the objection as the amendment corrects the minor informalities detailed in this objection. Therefore this objection is **withdrawn**.

Applicant's amendment, filed 19 Feb 2008, with respect to the objections regarding claim 4 has been fully considered and found to be persuasive to remove the objection as the amendment corrects the minor informalities regarding the drawing of a chemical structure in this objection. Therefore this objection is **withdrawn**.

The following rejections are reiterated and maintained.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 4 and 7-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for reducing the degenerative effects on cartilaginoid matrix, does not reasonably provide enablement for preventing degenerative effects on cartilaginoid matrix or relapses of degenerative effects on cartilaginoid matrix. The specification does not enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to use or make the invention commensurate in scope with these claims.

The Applicant's attention is drawn to *In re Wands*, 8 USPQ2d 1400 (CAFC1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) The nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention: A method of preventing or reducing the degenerative effects on cartilaginoid matrix comprising administering to a subject with arthritis an effective amount of one or more compounds of the formula disclosed in instant claim 1 or salts thereof.

The state of the prior art: Prevent is defined as "keep from happening or arising; make impossible". See provided definition of prevent (definition of prevent, WordNet, of record). There is no prior art disclosing making degenerative effects on cartilaginoid matrix or relapses of degenerative effects on cartilaginoid matrix impossible. Armour et al. (Arthritis and Rheumatism, provided by applicant as reference AN in IDS filed 08 Oct 2004) discloses "Although traditional NSAIDs are widely prescribed for the treatment of inflammatory and degenerative disorders of the musculoskeletal system, they do not

appear to exert major protective effects on bone loss in humans." (page 2191, right column, lines 23-27) and "Previous work has shown that HCT1026 [flurbiprofen nitroxylbutylester] retains the antiinflammatory and analgesic properties of the nonnitrosylated parent compound, flurbiprofen, but is less likely to cause gastrointestinal side effects. We show here that HCT1026 has additional advantages over the parent NSAID, in that it exerts potent inhibitory effects on osteoclast formation and bone resorption in vitro and prevents ovariectomy-induced bone loss in vivo." (page 2192, left column, lines 1-9) However, the data of Armour et al. discloses only the reduction of bone loss, as illustrated by the graphs in Figure 6 on page 2190, showing a percent change due to bone loss that is significantly different from 0. Absolute prevention, or making degenerative effects on cartilaginoid matrix or relapses of degenerative effects on cartilaginoid matrix impossible, is not disclosed.

The relative skill of those in the art: The relative skill of those in the art is high.

The predictability or unpredictability of the art: The lack of any prior art disclosing making degenerative effects on cartilaginoid matrix or relapses of degenerative effects on cartilaginoid matrix impossible means that one skilled in the art cannot predict the usefulness of a method to make degenerative effects on cartilaginoid matrix or relapses of degenerative effects on cartilaginoid matrix impossible. Therefore the claimed invention is unpredictable.

The Breadth of the claims: The scope of the claims specifically includes prevention of making degenerative effects on cartilaginoid matrix (instant claims 1, 3, 4 and 7-9) or relapses of degenerative effects on cartilaginoid matrix (instant claim 9).

The amount of direction or guidance presented: The specification speaks generally about inhibition of TNFα-induced inflammatory changes. See instant specification, page 31, lines 21-25. No limiting definition of "prevention" that would preclude the definition recited above is given.

The presence or absence of working examples: The only working examples provided are for reduction of IL-6 release. For example, see instant specification, example F3, page 35 and results in table 3, spanning pages 42-42.

Note that lack of working examples is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art such as preventing degenerative effects on cartilaginoid matrix or relapses of degenerative effects on cartilaginoid matrix. See MPEP 2164.

The quantity of experimentation necessary: In order to practice the invention with the full range of all possible treatment methods beyond those known in the art, (such as reducing the degenerative effects on cartilaginoid matrix) one skilled in the art would undertake a novel and extensive research program to show that the compounds of the formula disclosed in instant claim 1 made degenerative effects on cartilaginoid matrix or relapses of degenerative effects on cartilaginoid matrix impossible. Because this research would have to be exhaustive, and because it would involve such a wide and unpredictable scope of compounds and disease-affected subjects, it would constitute an undue and unpredictable experimental burden.

Genentech, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent protection is

granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors, as discussed above, particularly the breadth of the claims, Applicants fail to provide information sufficient to practice the claimed invention for **prevention** of degenerative effects on cartilaginoid matrix or relapses of degenerative effects on cartilaginoid matrix.

Response to Applicant's Remarks:

Applicant's remarks, filed 19 Feb 2008, have been fully considered and are not found persuasive to remove this rejection.

Applicant remarks that the progression of arthritic disease is due the imbalance between pro-inflammatory mediators (e.g., IL-6 and TNF-a) and anti-inflammatory mediators (e.g., TGF-13). As recited in the rejection above examples F1-F6 within the disclosure provide enablement for reducing the degenerative effects on cartilaginoid matrix. However, the definition of "prevent" provided in the rejection above encompasses making a thing impossible, and the examples do not provide evidence that an imbalance between pro-inflammatory mediators and anti-inflammatory mediators is made impossible. Similarly, no evidence is provided that relapses of degenerative effects on cartilaginoid matrix are made impossible. Further, the invention as claimed encompasses a method making all "degenerative effects on cartilaginoid matrix" impossible.

Therefore this rejection is **maintained**.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3, 4 and 7-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Armour et al. (Arthritis and Rheumatism, provided by applicant as reference AN in IDS filed 08 Oct 2004).

Armour et al. discloses HTC1026 or flurbiprofen nitroxylbutylester (page 2185, left column, lines 10-11), the elected species, administered in vivo using a mouse model of ovariectomy-induced bone loss (page 2185, left column, lines 16-17) to inhibit bone resorption (page 2185, right column, lines 3-4). For the structure of flurbiprofen, see attached entry from The Merck Index (The Merck Index, cited in PTO-892). Armour et al. discloses flurbiprofen nitroxylbutylester may be used for treatment of arthritis, characterized by joint inflammation as well as periarticular and systemic bone loss (page 2185, right column, lines 8-12). The disclosure of flurbiprofen nitroxylbutylester administered to a mouse model of ovariectomy-induced bone loss, a subject with arthritis, to inhibit bone resorption and treat periarticular and systemic bone loss, or reduce degenerative effects on the cartilaginoid matrix, anticipates instant claims 1, 3, 4, and 7. The phrase “degenerative effects on the cartilaginoid matrix” of instant claim 1 includes bone loss in a joint due to bone resorption. Armour et al. discloses administration of flurbiprofen nitroxylbutylester by intraperitoneal injections in corn oil (page 2186, right column, lines 7-9), anticipating parenteral administration disclosed in instant claim 8.

Response to Applicant's Remarks:

Applicant's remarks, filed 19 Feb 2008, have been fully considered and are not found persuasive to remove this rejection.

Applicant remarks that Armour et al. merely discloses the effect of HCT1026 on osteoclast cells in bones, and does not disclose any effect of HCT1026 on chondrocytes (the cells found in cartilaqe), much less reducing the degenerative effects on cartilaqinoid matrix as in the method of the presently claimed invention.

Armour et al. discloses administration of flurbiprofen nitroxylbutylester by intraperitoneal injections to a mouse model of ovariectomy-induced bone loss, a subject with arthritis, anticipating the active steps and treatment population of the instantly claimed method. While Armour et al. is silent to the effect of HCT1026 on chondrocytes found in cartilaqe, it apparent from what is disclosed that the effect of HCT1026 on chondrocytes is an inherent property of the method disclosed by Armour et al. "[T]he claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable", see MPEP 2112 I.

Further, with regard to whether bone loss in a joint is encompassed in the scope of the limitation "degenerative effects on cartilaqinoid matrix", the definition of "degenerate" in the context of pathology means "to lose functional activity" (definition of degenerate, Dictionary.com, cited in PTO-892). A cartilaginoid matrix exists within the cartilage of a joint, in contact with bone of the joint, such as a tibia. See illustration of a normal knee joint (synovial fluid entry, MedlinePlus, cited in PTO-892). Therefore, bone loss in a joint will cause an effect of some loss of functional activity of the cartilaginoid

matrix in that joint due to the intimate connection of the bone and the cartilage. The invention as claimed does not require the limitation of degeneration of the cartilage itself or an effect on chondrocytes, but rather "degenerative **effects** on cartilaginoid matrix", emphasis added. Therefore, broadly interpreted, Armour et al. anticipates "degenerative effects on cartilaginoid matrix" and discloses each element of the invention as claimed.

Therefore this rejection is **maintained**.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jonathan S. Lau whose telephone number is 571-270-

3531. The examiner can normally be reached on Monday - Thursday, 9 am - 4 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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